

► such tests would need to be developed.

But there is another, deeper, problem. Even when a drug's mechanism looks obvious, it sometimes is not. Erbitux, for example, binds to a cell-surface protein called epidermal growth-factor receptor (EGFR). This controls growth and survival pathways in cells. Many types of tumour produce far more EGFR than normal cells do, and one effect of that is to stimulate the proliferation of tumour cells. Researchers thought this meant the receptor would be central to the survival of those cancer cells, but that has not consistently been so.

Erbitux slows the progression of colorectal cancer, but the drug's activity does not correlate with expression of EGFR in such tumours. Its activity does, however, correlate with EGFR expression in lung cancer, according to data presented at the conference by Roy Herbst of the M.D. Anderson Cancer Centre in Texas. The cause of this contradiction is mysterious.

Even when the level of a molecule seems to predict a drug's success, a test may prove unreliable. One of the biggest success stories of targeted therapy is a drug

called Herceptin. This dramatically reduces the risk of relapse in breast-cancer patients whose tumours make a protein called Her2/neu, and only those women whose tumours produce this protein will respond to the drug.

That was proved two years ago, when three large trials showed Herceptin's value in treating early-stage Her2-positive breast cancer. However, recent re-tests of tissue taken at the time, and reported at the meeting, suggested that 10% of the tests which were originally positive for Her2/neu appeared negative on re-testing.

That is surprising, as many of these women responded to therapy. Nor is there any question over Herceptin's specificity—that is now well established. What is called into question is the reliability of the test. If a woman is denied treatment on the grounds that she could not possibly benefit, the basis of that denial had better be rock-solid. For the moment, the suggestion is that those who test negative should get a second opinion. But it all goes to show that what looks clean and simple in theory can be very complicated in practice. ■

Cosmology

A lithium imbalance

The universe's chemistry looks wonky. That may change the laws of physics

OUT of chaos comes order. Or at least it did in the early universe. Moments after the Big Bang, space was a hot, dense, seething froth of elementary particles and light. As the universe expanded and cooled, some of these particles merged to form neutrons and protons. When it had cooled further, these protons and neutrons were able to get together to form the nuclei of the lightest elements—hydrogen, helium and lithium. And so the stage was set for stars, nuclear reactions, chemistry and, eventually, life.

The exact abundances of the three lightest elements are an important test of the so-called Standard Model of physics—the list of fundamental particles found so far and the forces that link them. The Standard Model makes clear predictions for the ratios of various isotopes of all three. It gets the hydrogen and helium right. The values for lithium, though, are not.

This discrepancy is known to cosmologists as the "lithium problem" and, until now, there has been no satisfactory explanation for it. But Maxim Pospelov, of the Perimeter Institute for Theoretical Physics in Waterloo, Ontario, thinks he has one. And if he is right, he may have opened a window on to a theory of physics known as supersymmetry, which goes ►►

Molecular medicine

Peekaboo

The search for genes that cause disease bags some new trophies

ALTHOUGH cancer has become the improving ground of molecular medicine—the idea that proteins characteristic of a disease are the ones to aim at when designing therapies—the hope is that the approach will be more widely applicable than that. The first step towards realising this hope, of course, is to work out the nature of the molecules in question—and that is the purpose of a paper published this week in *Nature* by the members of the Wellcome Trust Case Control Consortium.

One of the goals of the Human Genome Project was to allow researchers to link versions of individual genes (known as alleles) with particular diseases. This has proved a lot harder than expected, because if lots of genes contribute to a disease, the signal from each is inevitably weakened. That means only large projects have much chance of working out what is going on. Hence the decision of Britain's biggest medical-research charity to put together the consortium that has just reported.

The researchers, all 256 of them, looked at seven diseases: bipolar disorder, coronary-artery disease, Crohn's disease (an inflammation of the gut), hypertension, rheumatoid arthritis, type I diabetes (the sort that develops early in life) and type II diabetes (the sort that de-

velops later). They studied 2,000 people with each condition and compared them with 3,000 symptom-free individuals. In each case they used devices called gene chips to look for associations between a disease and one or more of 500,000 so-called single-nucleotide polymorphisms (SNPs). These are places where the DNA of some individuals differs from that of others by a single molecular letter of the genetic code. Some SNPs occur in genes themselves. Others are found in the DNA between genes. But all act as markers that may be associated with different alleles of the same gene.

The result was the discovery of 24 places in the genome so strongly associated with a disease that there was only one chance in 2m of the link being accidental. A further 58 associations had less than one chance in 100,000 of being wrong. The richest targets were Crohn's disease and type I diabetes, with nine and seven near-certainties respectively.

Some of the candidates corresponded to known genes. Others did not, and the next phase of the project will be to search the areas of the genome that the SNPs point at for likely genetic suspects. Once these are discovered, the proteins they encode can be added to the lists of those that are targets for the molecular medicinal drug-makers.



▶ beyond the Standard Model.

Dr Pospelov's idea, which he explains in a paper in *Physical Review Letters*, depends on the main prediction of supersymmetry—or SUSY, as it is known to physicists. This is that each of the particles in the Standard Model has a heavier doppepartner known as its "superpartner".

If these superpartners do exist, SUSY suggests the Big Bang would have produced a lot of them. Dr Pospelov has taken this insight one step further. According to his calculations, the superpartners would have had a profound effect on the ease with which certain elements were produced in the early universe. This is because they would have combined with protons and neutrons in ways that made it easier and faster for other nuclear reactions to occur. Once they had had their catalytic effect, they would have split back off again and gone their own ways.

The most dramatic effect would have been on the formation of lithium, an element that has two isotopes. One of these has three protons and three neutrons (${}^6\text{Li}$). The other has three protons and four neutrons (${}^7\text{Li}$). According to Dr Pospelov, ${}^6\text{Li}$ would have formed 100m times faster in the presence of the heavy particles of supersymmetry than in their absence. In effect, ${}^6\text{Li}$ should not exist unless these extra particles are real. Meanwhile, reactions that deplete ${}^7\text{Li}$ should also have proceeded faster in a supersymmetric universe than in one that is governed only by the Standard Model. So if supersymmetry is true, there should be less of this isotope around than the Standard Model predicts.

This is exactly what astronomers have been observing for years in the real universe. Although ${}^6\text{Li}$ is rare, it does exist. As for ${}^7\text{Li}$, astronomers have measured only one-third to one-half of what the standard theory suggests should be there.

Until now, attempts to explain away the lithium problem have involved secondary modifications of the amount around. The extra ${}^6\text{Li}$ has been brushed away as the result of energetic particles from space crashing into the gas from which stars form. The lack of ${}^7\text{Li}$, meanwhile, has been blamed on over-hungry nuclear reactions in stellar cores.

Dr Pospelov's catalytic mechanism, by contrast, explains both discrepancies in one fell swoop. It also makes predictions about the detailed properties of the supersymmetric partners—and, as luck would have it, suggests that although they cannot be made on Earth at the moment, they should be in range of the Large Hadron Collider, a particle accelerator being built near Geneva, which should open for business later this year. It should not, therefore, take long to find out if his explanation for the lithium problem is correct. If it is, he can claim to have found SUSY's traces before the particle physicists did. ■

Archaeology

Rates of exchange

Some snail shells from a Moroccan cave could be humanity's earliest known attempt at art or, possibly, a currency

EXACTLY when humanity became artistic is much debated by palaeoanthropologists. But most acknowledge it was at least 75,000 years ago. The reason is the discovery, in 2004, of some peculiar sea-shells of that age in Blombos, a seaside cave in South Africa.

The shells are peculiar because they seem to have been fashioned into beads. They bear traces of red ochre, a pigment. They have been purposefully perforated, presumably to be strung together. And friction marks indicated that they did, indeed, once form part of a necklace or bracelet.

Now, though, some similar but even older beads have turned up at the other end of Africa, in Morocco. In this week's *Proceedings of the National Academy of Sciences*, Marian Vanhaeren and Francesco d'Errico of the National Centre for Scientific Research, in Nanterre, France, and their colleagues, describe a haul from about 82,000 years ago. Moreover, Dr Vanhaeren and Dr d'Errico think their discovery does more than push back the beginning of art. They believe it also hints at an ancient human society that may have developed a long-distance system of trade and cultural exchange.

The newly found beads come from a site called the Grotte des Pigeons. This is a large, hillside cavern about 40km (25 miles) from the sea. First Dr Vanhaeren and Dr d'Errico had to prove the snail shells found there could not have arrived by any means other than a human taking them. That meant showing, for instance, that no similar specimens are found in the cave walls, and that no predator of sea-snails could have deposited them there.

Next the researchers demonstrated that stone-age humans had meddled with the shells. Like the Blombos examples, they were all pierced in the same unnatural

way and covered in bits of ochre (which distinguished them from every other artefact recovered from the site). And they, too, had abrasion marks near these holes. Finally Dr Vanhaeren and Dr d'Errico dated the shells using four different techniques. All put them at between 74,000 and 91,000 years old, with 82,000 years the most likely date in the middle.

Such strands of evidence are shared with two sites the researchers investigated last year. But the snails from both of those sites—one in Israel and one in Algeria—were originally extracted in the 1930s, before the invention of modern dating methods. Their precise ages are thus debatable. Nonetheless, the Israeli and Algerian snails are probably roughly as old as those in the Grotte des Pigeons.

That the same snail species, *Nassarius gibbosulus*, was used to make the beads in both of the previously excavated Mediterranean sites is curious, but could have been a coincidence. The discovery of *Nassarius* beads at a third site suggests no coincidence is involved. It is more likely that the beads were either simply fashionable throughout the region, or that they acted as currency, as cowrie shells did in some parts of Africa until historical times.

Even more intriguingly, although the beads from Grotte des Pigeons are not from precisely the same species used at Blombos, the two are indistinguishable to the untrained eye. Stone-age South Africans, like their northern cousins, could have chosen any one of hundreds of shell shapes to make into beads, yet they adopted essentially the same fashion. The immense distance between the two ends of the continent makes an ancient African exchange system appear improbable. Then again, a chance predilection for the same beads is unlikely as well. ■



Jewels in the crown? Or dollars in the making?